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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 35/78, 31/70

A1

(11) International Publication Number: WO 97/29763

(43) International Publication Date: 21 August 1997 (21.08.97)

(21) International Application Number: PCT/US97/01665

(22) International Filing Date: 6 February 1997 (06.02.97)

(30) Priority Data:
08/601,482 14 February 1996 (14.02.96) US
08/630,096 9 April 1996 (09.04.96) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: UROGENITAL AND INTESTINAL DISORDER COMPOSITIONS COMPRISING A SUBSTANCE DERIVED FROM PLANT SPECIES OF THE ERICACEAE FAMILY AND A LACTIC ACID BACTERIA GROWTH FACTOR

(57) Abstract

This application relates to compositions useful in preventing and/or treating urogenital and intestinal disorders, comprising an effective amount of at least one plant species of the Ericaceae family or its extract and an effective amount of a growth factor for stimulating the growth of lactic acid bacteria, the growth factor selected from the group consisting of glycogen, rhamnose, gangliosides, salicin, oligosaccharides, galactose, lactulose, methyl-α-D-mannoside, ρ-nitrophenol-α-D-mannoside, maltose, dextrin, dextran, levan, sialic acid, acetylglucosamine, yeast extracts, peptone, keratin, vegetable, soy, lauric acid, glycerophosphates and mixtures thereof.

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UROGENITAL AND INTESTINAL DISORDER COMPOSITIONS COMPRISING A SUBSTANCE DERIVED FROM PLANT SPECIES OF THE ERICACEAE FAMILY AND A LACTIC ACID BACTERIA GROWTH FACTOR

TECHNICAL FIELD

This application relates to compositions useful in preventing and/or treating urogenital and intestinal disorders.

BACKGROUND OF THE INVENTION

Complex, microscopic ecosystems pervade the urogenital and intestinal tracts of warm blooded animals. Trillions of microorganisms, comprising hundreds of species, occupy the urogenital and intestinal tracts of mammals, influencing and maintaining digestive and urologic functions. Microorganisms occupying these regions range from potentially pathogenic strains, such as *Escherichia coli*, enterococci, candida, gardnerella, klebsiella and clostridia, to the relatively nonpathogenic, such as lactobacillus and bifidobacterium. Deviations from this delicate floral balance have been etiologically linked to a number of urogenital and/or gastrointestinal tract disorders; such imbalances usually resulting in the proliferation and predominance of pathogenic species. Establishing and/or preserving such a delicate floral balance is, therefore, essential to maintaining optimal health.

One way of establishing or maintaining the body's flora is by promoting the growth of lactic acid bacteria (e.g., lactobacillus or bifidobacterium). The use of growth factors to treat urogenital and intestinal disorders has been proposed, for instance, in Canadian Patent 1,298,556, issued April 4, 1992 and to Bruce et al., PCT Application Serial Number WO 93/09793, published May 27, 1993, to Reid et al. Ideally, such growth factors selectively provide lactic acid bacteria with nutrients and an environment essential for continued growth. Despite such selectivity, however, alternative nutrient sources remain available for pathogenic bacteria. Furthermore, growth substrates fail to provide direct activity against offending microorganisms. Therefore, notwithstanding such proposals, there still remains a need for improved urogenital and gastrointestinal tract compositions containing lactic acid bacteria growth factors.

The present inventors have found that compositions incorporating plants or extracts of the Ericaceae family with Lactobacillus and/or Bifidobacterium provide improved compositions for treating and/or preventing urogenital and gastrointestinal disorders by modifying the interaction of pathogens with cellular tissue. Recent studies also suggest the value of such extracts in treating urinary tract infections. Researchers

have observed that various species of Vaccinium (e.g. cranberry and blueberry) contain a high molecular weight compound that inhibits the adhesion of common urinary pathogens (e.g., *E. coli*) to infection sites within the urinary tract. Ofek I et al., Anti-Escherichia coli Adhesin Activity of Cranberry and Blueberry Juices, N Engl J Med 1991;324;1599. Surprisingly, the compositions of the present invention provide improved environments more conducive to the colonization of lactic acid bacteria.

Accordingly, it is an object of the present invention is to promote a healthy environment for the growth of lactic acid bacteria in the urogenital and gastrointestinal tracts.

Another object of the present invention is to provide improved compositions comprising a growth factor for lactic acid bacteria.

A further object of the present invention is to provide compositions for dietary supplementation.

A still further object of the present invention is to provide topical compositions for vaginal use.

An even further object of the present invention is to provide compositions and methods effective in preventing and/or treating urogenital and intestinal disorders.

These and other objects will become readily apparent from the disclosure which follows.

SUMMARY OF THE INVENTION

The present invention relates to compositions for the treatment or prevention of urogenital and intestinal disorders, comprising:

a.) at least one plant species of the Ericaceae family or its extract; and

b.) an effective amount of a growth factor for facilitating the growth of lactic acid bacteria selected from the group consisting of glycogen, rhamnose, gangliosides, salicin, oligosaccharides, galactose, lactulose, methyl-α-D-mannoside, ρ-nitrophenol-α-D-mannoside, maltose, dextrin, dextran, levan, sialic acid, acetylglucosamine, yeast extracts, peptone, keratin, vegetable, soy, lauric acid, glycerophosphates and mixtures thereof.

The phrase "urogenital and intestinal compositions," as used herein, means a product which in the ordinary course of usage may be retained in the oral cavity, swallowed or applied topically to provide urogenital and/or intestinal activity.

The term "urogenital," as used herein, means that system of organs concerned with the production and excretion of urine and reproduction.

The term "intestinal," as used herein, means of or relating to the intestines.

All percentages and ratios used herein are by weight unless otherwise specified. Also, all measurements referred to herein are made at 25°C unless otherwise specified.

DETAILED DESCRIPTION OF THE INVENTION

The essential as well as optional components of the compositions of the present invention are described in the following paragraphs.

ESSENTIAL COMPONENTS

Plant or Extract of the Family Ericaceae

The Ericaceae (heath) family, consisting of about 110 genera and 4,000 species, is by far the most important family of the Ericales order, encompassing a wide variety of fruit producing shrubbery and evergreen plants. Genera falling under Ericaceae family include Vaccinium, Arctostaphylos, Gaultheria, and Gaylussacia. The Arctostaphylos genus includes such species as the checkerberry and bearberry (*Uva ursi*). Other edible fruits such as the creeping snowberry or moxie plum fall under the genus Gaultheria. Huckleberries are a well known species of the genus Gaylussacia. The Vaccinium genus, best known for its fruits, contain some of the most common of berries, including the blueberry (e.g., *V. australe*), cranberry (e.g., *V. macrocarpon*) and bilberry (e.g., *V. myrtillus*). The term "berry (ies)," as used herein, means berries, drupes, plums and the like.

E. coli adherence results primarily from adhesins on the raised hair like fimbriae (or pili) of the microorganism. These adhesins are designated MS (mannose-sensitive) and MR (mannose-resistant). Like most fruit, Ericacease fruit species contain fructose, an inhibitor of MS adhesins. However, it has been recently suggested that the plants or extracts of Ericaceae species further contain an unidentified, non-dialyzable polymeric compound which inhibits the MR adhesins associated with pyelonephritogenic strains of *E. Coli*. The unidentified polymeric compound, as studied in Vaccinium species, was found to inhibit both urinary and fecal isolates of *E. Coli*, the urinary isolates being inhibited to a greater extent. Ofek, I. et al., Anti-Escherichia coli Adhesin Activity of Cranberry and Blueberry Juices, N Engl J Med 1991;324;1599. It has also been reported that the ingestion of large quantities of cranberry juice increased the hippuric acid content of urine by several grams a day. This increase in hippuric acid excretion was accompanied by small decreases in urine pH. *In vivo* tests have established that hippuric acid was bacteriostatic at pH 5.0 for common pathogens of the urinary tract, but this action was considerably decreased as the urine pH was raised. Papas, N.P., et al., Cranberry Juice In the Treatment of Urinary Tract Infections, Southwestern Medicine, 47:No. 1 (Jan. 1966). That the Ericaceae species of the present invention are effective against other pathogenic

bacteria (e.g., Pseudomonas aeruginosa) is disclosed in U.S. Patent 5,474,774, herein incorporated by reference in its entirety; no effect was observed with respect to adhesion of lactobacillus strains to cells. Without being limited by theory, it is believed that the pathogenic inhibition caused by the Ericaceae plants or extracts results in decreased pathogenic interaction, providing a more favorable, less antagonistic environment for lactobacillus to initially adhere and maintain adherence. The phrase "anti-adhesive activity," as used herein, means an amount effective to inhibit the adhesion of pathogenic microorganisms to the epithelial and/or mucosal lining of the urogenital and/or intestinal tract.

Plants or extracts useful in the compositions of the present invention come from a wide range of genera within the Ericaceae family including, but not limited to, Vaccinium, Arctostaphylos, Gaultheria, and Gaylussacia. Preferred species include, *V. australe, V. corymbosum, V. occidentale, V. ovatum, V. myrtillus, V. parvifolium, V. uliginosum, V. macrocarpon, V. oxycoccus, V. erythrocarpum, V. vitis-idaea. V. australe, V. macrocarpon*. Vaccinium species most preferred for use in the present invention include *V. australe, V. macrocarpon, and V. myrtillus*. Mixtures of Ericaceae plants and/or extracts may also be used.

The plants or extracts of the present invention are preferably concentrated, having a ratio of at least about 4 pounds of plant concentrate or extracts per pound of concentrate, more preferably from about 4 pounds of plant concentrates or extracts per pound of concentrate to about 50 pounds of plant concentrate or extracts per pound of concentrate. The Ericaceae extracts are preferably present at a level of at least 10mg, more preferably from about 100mg to about 18g, most preferably from about 250mg to about 4g per unit dose. The amount of extract contained in each dose of product can be adjusted for the dosage form. For example, the amount of extract in powdered form used in a drink mix can range up to 18g per dose while the amount used in swallowable capsules might range to about 4g. Preferred levels of the Ericaceae plants or extracts provide urinary and/or intestinal tract fluid concentrations of the above mentioned unidentified, non-dialyzable polymeric compound of from about 12 to about 25 micrograms per milliliter. Also, the plants or extracts of the present invention preferably retain greater than 2.5% of their total acid content and greater than about 0.1% of their benzoic acid content. The level is selected to provide the desired level of anti-adhesin activity and can be modified as desired. Cranberries and cranberry extracts are useful in the treatment and/or prophylaxis of urinary tract infections and are also useful as vaginal deodorants.

Growth Factor for Lactic acid Bacteria

The compositions of the present invention also incorporate a growth factor for lactic acid bacteria. The phrase "a growth factor for facilitating the growth of lactic acid bacteria," as used herein, means a nutrient source or media which supplies a necessary source of food and/or energy for facilitating the growth of lactic acid producing bacteria. The growth factor is preferably selective for establishing and maintaining the growth of lactic acid bacteria, preferably Lactobacillus and/or Bifidobacterium species, without facilitating extreme growth of pathogenic bacteria. The various nutritional requirements essential for bacterial and/or colony growth are normally met when the growth factor contains fermentable carbohydrate, peptone, meat or yeast extract. Supplementations with tomato juice, manganese, acetate and oleic acid esters, especially Tween 80, are stimulatory or even essential for most species and are, therefore, included in most MRS medium. Lactic acid bacteria adapted to very particular substrates may require special growth factors.

Growth factors suitable for use in the present invention are selected from the group consisting of glycogen; D-mannose; mannitol; esculine; lactose; saccharose; trehalose; D-raffinose; gentibiose; gluconate; rhamnose; gangliosides; salicin; oligosaccharides; galactose; lactulose; methyl-α-D-mannoside; ρ-nitrophenol-α-D-mannoside; maltose; dextrin; maltodextrin; dextran; levan; sialic acid; acetylglucosamine; yeast extracts; proteinacious materials such as, peptone, keratin; vegetable; soy and unsaturated fatty acids such as lauric acid and teichoic acids such as lipoteichoic acid and esters such as glycerophosphates or β-glycerophosphates. Fiber or fermentable substrates such as psyllium may be used in the present compositions as may gums such as guar gum and xanthan gum. When used vaginally monosaccharides such as fructose and glucose as well as whey proteins may also be incorporated. The growth factor is preferably selected from the group consisting of rhamnose, oligosaccharides and glucogen.

More preferably the growth factor of the present invention is an oligosaccharide such as, but not limited to, galactooligosaccharides, soybean oligosaccharides and fructooligosaccharides. In addition to being a carbohydrate source, oligosaccharides also possess bioadhesive properties which help fix the location of these growth factors for easier access by lactic acid bacteria. Most preferred for use herein are fructooligosaccharides. Lactic acid bacteria, such as Lactobacillus and Bifidobacterium, partially utilize fructooligosaccharides as an energy source by converting it, via fermentation, to lactic acid or a mixture of lactic acid, acetic acid, and CO_2. The lactic acid and other fatty acids produced by this carbohydrate fermentation contribute to the

maintenance of low pH which is an important control mechanism for preventing colonization of pathogens.

Chemically, oligofructose is the oligosaccharide fraction of inulin. It is composed of the GFn and Fn type [G = glucose; F = fructose; n = number of frets moieties linked by β (2,1) linkages in a ratio of about 2:1, with n = 2-6, and an average degree of polymerization of 4. Inulin is prepared by hot water extraction of chicory roots and is composed of molecules of the GFn type, n ranging as high as 60 with an average degree of polymerization of 10. Fructooligosaccharides suitable for use herein may or may not have non-fructosyl units in place of fructosyl end units. The same is true for other oligosaccharides with respect to their osyl end units. Non-fructosyl units may include, but are not limited to, polyalcohols such as xylitol, mannitol, and sorbitol. Fructooligosaccharides most preferred for use in the present compositions are inulin or oligofructose. Mixtures of these nutrients may also be used.

Without being limited by theory, it is believed that, upon ingestion, growth factors increase the number of Lactobacillus and/or Bifidobacterium species available to displace pathogenic microorganisms from epithelial surfaces. The increase in the number of Lactobacillus and/or Bifidobacterium species competitively exclude the pathogens causing them to be displaced and excreted; the result is an overall reduction of host pathogens. Moreover, as vaginal infections are generally believed to result from pathogenic migrating from the rectum to the vagina, the number of pathogens invading the vagina are also reduced as the number of migratory pathogens decreases.

Growth factors are preferably incorporated into the compositions of the present invention at from about 5% to about 75%, more preferably from about 20% to about 70%, and most preferably from about 30% to about 65% per unit dose.

OPTIONAL COMPONENTS

Species of Lactobacillus or Bifidobacterium

An optional component of the present invention is a viable colony of Lactobacillus or Bifidobacterium. Bacteria of the Lactobacillus genus are characterized as rod-shaped, gram-positive and non-spore-forming bacteria. Of the family Lactobacillaceae, Lactobacillus inhabit the urogenital and gastrointestinal tracts of animals and humans and are important members of lactic acid producing group of bacteria. Various species of Lactobacillus are used commercially in the production of sour milks, cheeses and yogurt. Lactobacilli also share an important role in the manufacture of fermented vegetables (e.g., pickles and sauerkraut), beverages (e.g., beer, wine and juices), sourdough breads, and some sausages.

Lactobacillus species suitable for use in the present invention are those which 1.) readily adhere to the epithelial cells of either the urogenital or gastrointestinal tracts of mammals; 2.) produce hydrogen peroxide; 3.) promote low pH; and produce bacteriocins. By "bacteriocins," as used herein, means proteinaceious, bacteriocidal substances synthesized by bacteria, which usually have a narrow spectrum of activity, inhibiting strains of the same or closely related species. Bacteriocins appear to be capable of displacing or suppressing the growth of other bacteria, and as such may provide an advantage to microorganisms in fermenting the female genital tract ecosystem. Preferred species of Lactobacillus include *L. acidophilus, L. johnsonii, L. catenaforme, L. brevis, L. bulgaricus, L. lactis, L. reuterii, L. gasseri, L. helveticus, L. casei, L. plantarum, L. delbrueckii, L. thermophilis, L. jensenii, L crispatus, L. rogosae and L. fermentum.* Species of Lactobacillus most preferred for use in the compositions of the present invention include *L. acidophilus, L. casei, L. crispatus, L. fermentum, and L. plantarum.* Preferably, the Lactobacillus species of the present invention are hydrogen peroxide producing such as *L. acidophilus, L. catenaforme, L. casei, L. crispatus, L. delbrueckii, L. jensenii, L rogosae. L. fermentum, L. gasseri and L. plantarum* are also preferred for use herein in view of their adhesive properties.

Also inhabiting the urogenital and gastrointestinal tracts of mammals and useful to the compositions of the present invention are species of the genus Bifidobacterium (family Actinomycetaceae). Bifidobacterium species are non-acid-fast, nonmotile gram negative rods. Lactic and acetic acid producing Bifidobacteria are also considered important regulators of the urogenital and intestinal flora of mammals. Species suitable for use in the present compositions include, but are not limited to, *B. longum, B. breve, Lactobacillus Bifidus* and *Lactobacillus bifidus subsp pennsylvanicus.* Preferred for use in the present compositions is *B. Bifidum*, most preferred *B. Bifidum subsp. Pennsylvanicus.*

Mixtures of the Lactobacillus and/or Bifidobacterium species may also be used. Any of the above species may be obtained either commercially or through laboratory cultures.

The Lactobacillus and/or Bifidobacterium species are present at levels of at least about 10^3 cells per unit dose, preferably at levels of from about 10^4 to about 10^{12} cells per unit dose and most preferably at levels of from about 10^6 to about 10^{10} cells per unit dose. The phrase "unit dose," as used herein, means physically discrete units suitable as unitary dosages for administration to mammals, each such unit containing a predetermined quantity of an active ingredient calculated to produce the desired therapeutic effect in association with pharmaceutically acceptable carriers. The level is selected to provide the

desired level of urogenital and gastrointestinal activity and can be modified as desired. Lactobacillus may loose 4-6 fold of its viability at room temperature and during manufacturing, so depending on the manufacturing conditions, an excess of Lactobacillus is added to maintain an adequate number of viable organisms per final unit dose form. Alternatively, a patient can be administered the equivalent of these concentrations of organisms where the values are expressed by some other measurement such as, for example, total protein concentration.

Buffering Agents

The compositions of the present invention may also contain a buffering agent. For oral compositions, buffering to an acidic pH to enhance flavor may be done. For products used in the vaginal area, buffering agents suitable for use in the compositions of the present invention are those capable of maintaining a urogenital pH of 3.0 to 5.5. Any mild pharmaceutically acceptable acid, other than those found in the Ericaceae species disclosed herein, can be used. Suitable acids include boric acid, or organic acids such as quinnic acid, proprionic acid, malic acid, pyruvic acid, hippuric acid, tartaric acid, sorbic acid, benzoic acid, lactic acid, ascorbic acid, citric acid, or acetic acid, in combination with their respective sodium or other pharmaceutically acceptable salt (to the extent necessary to achieve the desired pH). When buffered, the compositions of the present invention are preferably buffered to a pH range of from about 3.5 to about 5.0, preferably from about 3.7 to about 4.7, and preferably using lactic acid with sodium lactate or a combination lactic acid/sodium lactate and benzoic acid or lactic acid/sodium lactate and proprionic acid.

Additional Plant Extracts

Additional therapeutic and/or medicinal plants or extracts may also be incorporated into the compositions of the present invention. Such plants or extracts include echinacea, allium, bucha, juniper ginseng, allicin, chlorella, algin and the like. Mixtures of these additional plants or extracts may also be used.

Nutritional Additives

Nutritional additives may also be incorporated into the compositions of the present invention. Such additives include, but are not limited to, proteins and carbohydrates other than those mentioned herein as growth factors, vitamins such as nicotinic acid, pantothenic acid, and riboflavin; minerals such as manganese; phytochemicals; amino acids such as serine, glutamine, methionine, glycine, cysteine, leucine, isoleucine, threonine, valine.

Pharmaceutical Actives

The compositions of the present invention may also be used in combination with pharmaceutical actives. The pharmaceutical active is preferably selected from at least one of an analgesic agent and/or a gastrointestinal agent.

Examples of analgesics preferred for use in the present invention include acetaminophen, acetyl salicylic acid, indomethacin and optically active isomers or racemates of ibuprofen, naproxen, flurbiprofen, carprofen, tiaprofenic acid, cicloprofen, ketoprofen, ketorolac, etodolac, indomethacin, sulindac, fenoprofen, diclofenac, piroxicam, benzydomine, nabumetone, their pharmaceutically acceptable salts and mixtures thereof.

Examples of gastrointestinal agents preferred for use in the present invention include anticholinergics including atropine, clidinium and dicyclomine; antacids including aluminum hydroxide, bismuth subsalicylate, bismuth subcitrate, simethicone, calcium carbonate and magaldrate; H_2-receptor antagonists including cimetidine, famotidine, nizatidine and ranitidine; laxatives including: docusate, phenolphthalein and casanthrol; gastroprotectants including sucralfate and sucralfate humid gel; gastrokinetic agents including metoclopramide and cisapride; proton pump inhibitors including omeprazole and antidiarrheals including: diphenoxylate, kaolin pectin, attapulgite and loperamide.

Carrier Materials

The carriers into which the compositions of the present invention may be incorporated are many and varied and depend largely upon the end use of the compositions. These carriers include orally acceptable as well as topical compositions. They may be completely inert or contain or may be other active ingredients, yet the carriers must be compatible with the herein disclosed compositions. The term "compatible," as used herein, means that the carrier components are capable of being commingled with the components of the present invention, and with each other, in a manner such that there is no interaction which would substantially reduce the activity of the compositions under ordinary use situations. Carrier materials must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human being treated. Preferably the compositions of the present invention comprise from about 0.01% to about 99.99% of one or more carrier materials.

Carriers suitable for topical administration of the present compositions include suppositories, vaginal tablets or capsules, ovules, creams, solutions for lavages, emulsions, foams, soaps, gels, liniments, oils and ointments.

Creams and gels, other base formulations may be used in topical administration of the present compositions to, for example, the genital region and are prepared according to conventional methods for semi-solid compositions using excipients like vaseline, paraffin, vaseline oil, vegetable oils, animal oils, solid and liquid synthetic glycerides, waxes, lanolin, lanolin alcohols, sorbitan esters, fatty alcohols, liquid/solid polyethylene glycols, propylene glycols, polyethylene, starch, acrylamides, methacrylamides, derivatives of cellulose and carboxyvinylpolymers.

Ovules, suppositories, vaginal capsules or tablets and effervescent tablets may also be useful in topical application of the prevention. Ovules are similar to suppositories, ovoidal shaped and the excipients mainly used are semi-synthetic glycerides and polyethylene glycols and optionally also emulsifiers and surfactants.

The vaginal capsules are gelatinous envelopes or sachets within which is subdivided the suspension which is generally anhydrous and contains liquid paraffin, vaseline, vegetable oils and semi-synthetic oils and thickening agents. The tablets, shaped suitably for vaginal use, contain as main excipients lactose, starch, polyvinylpyrrolidone, cellulose derivatives, magnesium stearate, glycol. The effervescent tablets contain chemical components (i.e. sodium bicarbonate with citric acid or tartaric acid), which are necessary to develop carbon dioxide in order to produce effervescence.

The compositions of the present invention may also be incorporated into and topically applied by woven or nonwoven fabric materials such as tissues, wipes, feminine napkins, panty liners, tampons, diapers, incontinent care products and the like. Preferred for use herein are nonwoven fabrics. Nonwoven fabrics suitable for incorporating the present compositions are described in U.S. Patent 4,891,227 to Thaman et al., herein incorporated by reference.

Oral dosage forms are also useful as carriers for the present invention. These dosage forms contain compatible solid or liquid filler diluents or encapsulating substances which are suitable for oral administration to a human or lower animal.

Liquid dosage forms for oral administration may comprise dissolving or suspending the compositions of the present invention in a potable liquid, such as sterile or distilled water. Alternatively, liquid or dry oral administration forms can comprise an enterically coated capsule containing the dosage forms. Suitable forms include emulsions, suspensions, solutions, syrups, and elixirs containing inert diluents commonly used in the art, such as purified water, sugars, polysaccharides, silicate gels, gelatin, or an alcohol. These inert diluents do not actively participate in the therapeutic effect of the present invention. Besides the inert diluents, such compositions can also contain wetting agents,

emulsifying agents, suspending agents, as well as additional therapeutic actives. For a more detailed description of liquid and liquid-like dosage forms, see Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa. (1990), pages 1519-1544, herein incorporated by reference.

Tablets can be compressed, molded, triturated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, and flow-inducing agents.

Tablets may be enteric-, film- or sugar-coated Protein-like coating components may also be included. Useful for improvement of gastrointestinal disorders, such components may contain branched amino acid-modified proteins. Whey powders, for example, are treated with papain in the presence of the amino acids ethyl L-leucine (16.1 parts), ethyl L-isoleucine (7.4 parts), ethyl L-valine (10.2 parts), cysteine hydrochloride (1.5 parts), and sodium carbonate (26 parts) in water at 40°C for 20 minutes to manufacture coated powders containing 10% free amino acids and 43% branched amino acids. The branched amino acid-modified powders can be mixed with fats, dextrins, salts, vitamins, and the like to make tablets.

Other examples of a tablet coating materials are zeolites and clays to make tablets more palatable. Zeolites have found use as bacterial feed coatings for domestic animals. For example, in the domestic animal business, timeline fumarate is dissolved in methanol, supported on mordenite-type zeolite or starch, dried and further premixed with the supports to produce sustained-release, coated granules. Still other examples of tablet coatings include complex carbohydrate and inclusion complexes.

Also useful are soft or hard gelatin capsules. Preferably, the gelatin shell is essentially transparent so as to enhance the aesthetic qualities of the capsule. Soft and hard gelatin shells generally comprise gelatin, a plasticizer and water. The starting gelatin material generally used in the manufacture of these capsules is obtained by the partial hydrolysis of collagenous material. Gelatin suitable for capsule manufacture is commercially available from the Sigma Chemical Company, St. Louis, Mo. One or more plasticizers is incorporated to produce a gelatin shell. Useful plasticizers of the present invention include glycerin, sorbitan, sorbitol, or similar low molecular weight polyols, and mixtures thereof.

Techniques and compositions for making solid oral dosage forms are described in Marshall, "Solid Oral Dosage Forms," Modern Pharmaceutics, Vol. 7, (Banker and Rhodes, editors), 359-427 (1979), incorporated by reference herein. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin), troches and pills are described in Remington's Pharmaceutical Sciences (Arthur

Osol, editor), 1553-1593 (1980) and U.S. Patent 4,935,243, to Borkan et al., issued June 19, 1990; these two references being incorporated herein by reference in their entirety. Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms, are described in U.S. Patent 3,903,297, Robert, issued September 2, 1975, incorporated by reference herein.

Alternatively, the compositions of the present invention may be achieved by incorporating the compositions of the present invention into freeze-dried or lyophilized tablets. Freeze-drying or lyophilization facilitates disintegration of the composition by forming the dried composition into an open matrix network. In most cases, this results in rapid permeation by the aqueous media, promoting timely delivery of the product. Suitable methods of freeze drying are well known in the art and commonly employed. Any suitable conventional method of freeze-drying may be utilized. A preferable method of freezing and drying is to fast freeze the composition and then dry the composition to a final moisture content of about 2% to about 5%. Suitable methods of freeze-drying and production are taught by U.S. Patent 4,642,903, February 17, 1987, to Davies, U.S. Patent 4,946,684, August 7, 1990, to Blank et al., U.S. Patents 4,305,502 and 4,371,516, issued December 15, 1981 and February 1, 1983 respectively, to Gregory et al., and U.S. Patent 5,188,825, February 23,1993, to Iles et al.; which are all incorporated herein by reference.

Similarly, the compositions of the present invention may be vacuum dried. Vacuum drying involves at least the partial drying of compositions at temperatures above compositions' collapse temperature. Freeze drying, on the other hand, involves the drying of compositions at temperatures below the composition's collapse temperature. Any suitable method of vacuum drying may be used. Suitable vacuum drying processes are described in U.S. Patent 5,298,261, to Pebley et al., issued March 29, 1994, herein incorporated by reference.

One other form of tableting technology that may be applicable to the present invention is a liquid/liquid extract developed by Janssen Pharmaceutica Inc. and is identified by the trade name Quicksolv™. This technology is fully described in U.S. Patent 5,215,756, herein incorporated by reference.

Other optional ingredients well known to the pharmacist's art may also be included in amounts generally known for these ingredients, for example, natural or artificial sweeteners, flavoring agents, colorants, perfuming agents, buffering agents and the like to provide a palatable and pleasant looking final product, antioxidants, for example, butylated hydroxy anisole or butylated hydroxy toluene, and preservatives, for example, methyl or

propyl paraben, potassium sorbate, or sodium benzoate, to prolong and enhance shelf life. A preferred optional component is also caffeine.

Those of ordinary skill in the art will quickly realize other suitable ingredients, diluents and dosage forms, or will be able to ascertain such, using routine experimentation. Further, the administration of the various compositions can be carried out using standard techniques common to those of ordinary skill in the art.

Examples

The following examples further describe and demonstrate embodiments within the scope of the present invention. These examples are strictly given for illustration purposes and are not to be construed as limitations of the present invention, as many variations are possible without departing from the spirit and scope of the invention as set forth herein.

Example I

A tablet form of the present invention is made by combining the following components using conventional mixing and tableting technology.

Ingredient	% Weight
Concentrated Cranberry Extract	17.600%
fructooligosaccharide[1]	56.340%
Ethylcellulose, 100 cps (5% ethanol soln)	9.900%
Starch	11.230%
Talc	4.230%
Stearic Acid	0.700%

[1] Available as NutraFlora FOS from Golden Technologies Company, Inc.

The cranberry extract and fructooligosaccharide are granulated with 5% ethylcellulose in ethanol. The granulation is then passed through a 12 mesh screen and dried at 120°F. To the dried granulation is added stearic acid. The granulation mixture is passed through a 20 mesh screen. To the sieved granulation is added the starch and talc and mixing until uniform. The resultant granulation mixture is then compressed using conventional tableting processes.

Example II

A capsule form of the present invention is made by combining the following components using conventional mixing technology.

Ingredient	% Weight
Concentrated Cranberry Extract	35.000%
fructooligosaccharide[1]	35.000%
Avicel[2]	26.300%

Ac Di Sol[3]	3.700%

[1] Available as NutraFlora FOS from Golden Technologies Company, Inc.

[2] TM for microcrystalline cellulose, a highly purified particulate form of cellulose.

[3] A brand of a cross-linked form of sodium carboxymethylcellulose.

Combine and mix the cranberry extract, fructooligosaccharide, Avicel and Ac Di Sol in a V-blender until uniform. Unit dose amounts of the resultant mixture is then placed into suitably sized hard gelatin capsules.

Example III

A topical gel form of the present invention is made by combining the following components using conventional mixing technology.

Ingredient	% Weight
Concentrated Cranberry Extract	0.50%
fructooligosaccharide[1]	6.00%
Polyacrylamide and C_{13-14} Isoparaffin and Laureth-7[2]	4.00%
PPG-14 Butylether	8.00%
Water, Purified	q.s.

[1] Available as NutraFlora FOS from Golden Technologies Company, Inc.

[2] Available as Sepigel from Seppic Corporation.

Water is added to a suitable size container. While mixing at a moderate speed (300 rpm), the Polyacrylamide and C_{13-14} Isoparaffin and Laureth-7 is added to the water to form a water phase. Separately, the PPG-14 Butyl ether is placed in a container and covered. Using a Lightnin' Mixer with a 3 blade paddle prop, the cranberry extract and fructooligosaccharide are added to the PPG-14 Butyl ether and mixed at a low speed (100 rpm) until the cranberry extract and fructooligosaccharide are dissolved. The PPG-14 Butyl ether mixture is slowly added to the water phase to form a gel. The resulting gel is mixed at moderate speed until uniform.

Furthermore, the above described compositions may also contain a growth factor such as glycogen, rhamnose, oligosaccharides, lactulose, methyl-α-D-mannoside, ρ-nitrophenol-α-D-mannoside, maltose, dextrin, levan, acetylglucosamine, amino acids, proteinacious materials such as, peptone, keratin, vegetable, soy, glycerophosphates and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

While the invention has been described in terms of its preferred embodiments, those skilled in the art will recognize that the invention can also be practiced by administering the herein described components separately and still remain within the scope and spirit of the present invention.

WHAT IS CLAIMED IS:

1. A composition for treating urogenital and intestinal disorders, comprising:
 a.) at least one plant species of the Ericaceae family or its extract; and
 b.) an effective amount of a growth factor for facilitating the growth of lactic acid bacteria selected from the group consisting of glycogen, rhamnose, gangliosides, salicin, oligosaccharides, galactose, lactulose, methyl-α-D-mannoside, ρ-nitrophenol-α-D-mannoside, maltose, dextrin, dextran, levan, sialic acid, acetylglucosamine, yeast extracts, peptone, keratin, vegetable, soy, lauric acid, glycerophosphates and mixtures thereof.

2. A composition according to Claim 1, further comprising a viable culture of at least one species of bacteria selected from the group consisting of lactobacillus, bifidobacterium and mixtures thereof.

3. A composition according to Claims 1 or 2 wherein growth factor is an oligosaccharide selected from the group consisting of galactooligosaccharides, soybean oligosaccharides, fructooligosaccharides and mixtures thereof.

4. A composition according to any one of the preceding Claims, wherein the plant or extract is from species selected from the genus selected from the group consisting of Vaccinium, Arctostaphylos and mixtures thereof.

5. A composition according to any one of the preceding Claims, further comprising an additional plant extract selected from the group consisting of echinacea, allium, bucha, juniper ginseng, allicin, chlorella, algin and mixtures thereof and/or a nutritional additive selected from the group consisting of proteins, carbohydrates, vitamins, minerals, amino acids, phytochemicals and mixtures thereof and/or a pharmaceutical active selected from the group of consisting of analgesics, gastrointestinal actives and mixtures thereof.

6. A composition according to any one of the preceding Claims, further comprising a carrier selected from group consisting of tablet, troche, oral liquid, suspension, capsule, gelatin capsule.

7. A topically administered composition for treating urogenital disorders, comprising:
 a.) at least one plant species of the Ericaceae family or its extract; and
 b.) an effective amount of a growth factor for facilitating the growth of lactic acid bacteria selected from the group consisting of glycogen, rhamnose, oligosaccharides, lactulose, methyl-α-D-mannoside, ρ-nitrophenol-α-D-mannoside, maltose, dextrin, levan, acetylglu-cosamine, proteinacious materials such as, peptone, keratin, vegetable, soy, glycerophosphates and mixtures thereof.

8. A composition according to Claim 7, wherein the growth factor is an oligosaccharide selected from the group consisting of galactooligosaccharides, soybean oligosaccharides, fructooligosaccharides and mixtures thereof.

9. A composition according to Claim 7 or 8, further comprising a buffering agent and wherein the composition is buffered to a pH of from about 3.5 to about 5.

10. A composition according to any of Claims 7, 8, or 9, further comprising a carrier selected from group consisting of suppository, vaginal tablet, vaginal troche, vaginal gelatin capsule, cream, gel, ointment, lotion, irrigant, douche, tissue, wipe, panty liner, feminine napkin, tampon, diaper and incontinent care product.

INTERNATIONAL SEARCH REPORT

Ir .tional Application No
PCT/US 97/01665

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K35/78 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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P,X	DATABASE WPI Week 9713 Derwent Publications Ltd., London, GB; AN 97-139596 XP002030869 & JP 09 019 276 (FUYO BUSSAN KK) , 21 January 1997 see abstract & JP 09 019 276 A (FUYO BUSSAN KK) 21 January 1997 ---	1,3,5,6
X	DE 34 27 014 A (MOSER H.H.) 23 January 1986 see page 3, line 17-20; claims 1,2,4,5 see page 61-22 --- -/--	1,4-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 May 1997	29. 05. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Kanbier, D

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INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/US 97/01665

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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